A hybrid multi-modal computer-aided diagnostic tool for improving diagnostic accuracy in breast cancer classification

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Keywords: breast cancer, pattern recognition, CADMAMMO, ARCHIMEDES project.

Abstract

The aim of this study was to design, develop and implement a hybrid multi-modal (radiological and microscopic imaging) computer-aided diagnostic tool for improving diagnostic classification of patients' breast cancer tumors. Results show that the most important single category of features is the textural features on the microscopy images with 87.3% prediction rate. When features from all families were concurrently tested, prediction accuracy was boosted up to 88.7% using a combination of five (5) textural, architectural and radiological features.

Introduction

Breast cancer is the most frequent malignant tumour among women and the fifth most common cause of cancer death. Diagnostic mammography is the most important and reliable screening method for confirming the location, extent, and other important clinical features of breast tumours (del Junco et al., 2008). Among the most important signs, indicating the presence of malignant lesions, are the existence of masses, microcalcifications (mCs) and clusters of mCs (Carney et al., 2010). However, in early stage cancer, the subtle differences between normal and abnormal tissues have been proven challenging for viewing even by experienced physicians (Buist et al., 2011, Jorgensen, 2010); up to 30% of breast lesions are missed during routine diagnosis (Cheng et al., 2003, Morrell et al., 2010). This is one of the reasons why mammograms are considered to be among the most difficult to interpret types of medical images. Another important reason is the low contrast appearance of early stage abnormalities (such as mCs) and their low differentiation from the surrounding breast tissues (Nakayama et al., 2009). Microcalcifications should appear as bright spots, however, in many cases, due to the composition of surrounding breast tissues and imaging limitations, mCs appear as low contrast entities. Even though mammography has dramatically improved over the past years, in many cases of breast lesion(s) diagnosis may be uncertain. Additionally, although imaging findings may indicate the existence of an abnormality, however, the actual diagnosis might not be obvious. Even when an abnormality is obvious, radiological findings cannot be solely used for predicting the course of the disease or for specifying of the treatment planning (Lester, 1984). In the presence of suspected lesion(s), pathologists are called to reach the final diagnostic conclusion on the basis of visual evaluation of microscopic material (histological

and/or cytological) under the microscope for the clarification of the importance of certain biological factors, such as histological tumour grade and estrogen receptor (ER) status (Allred et al., 1998, Spitale et al., 2009). Grading is determined on the visual estimation of certain histological features, such as glandular differentiation, nuclear pleomorphism, and mitotic count, on H&E (Hematoxylin & Eosin) stained specimens according to the World Health Organization (WHO) guidelines (Love, 2002, Allred et al., 2001), whereas ER-status is assessed as the percentage of expressed nuclei on immunohistochemically stained (IHC) specimens as suggested by the American Society of Clinical Oncology (ASCO) protocol (Diaz et al., 2004). Although microscopic examination is a critical process for treatment planning, the potential of diagnostic errors still remains substantially high; even the most experienced pathologist's diagnosis is sometimes a biased opinion, based on experience and on loosely defined classification criteria. Factors that affect diagnostic accuracy include (Allred et al., 2001, Bueno-de-Mesquita et al., 2010) experts' subjectivity and lack of experience, inter observer diagnostic variability, tumours' heterogeneity – (the higher the degree of malignancy the more heterogeneous is the composition of the tumour, the fact that tumours develop along a morphological and biological continuum, and poor sampling of tumour's tissues) so that not always the most representative tissue region is selected for examination.

Recent literature has highlighted that diagnostic, prognostic, and predictive misinterpretations in breast cancer management can be reduced by combining information from both radiological and microscopy findings (Ariga et al., 2002, Veta et al., 2014, Tan et al., 2015). However, to the best of our knowledge, no attempt for quantification, analysis, and computer-based interpretation of the integrated information from mammography and tissue/cytological imaging has been reported in literature.

The aim of this study is to design, develop and implement in the clinical routine a hybrid multi-modal (radiological and microscopic imaging) computer-aided diagnostic tool for improving diagnostic, prognostic, and predictive classification of patients' breast cancer tumors. This hybrid-multi modal tool was developed under the project CADMAMMO, which has been co-funded by the European Union (European Social Fund) and Greek national resources under the framework of the "Archimedes III: Funding of Research Groups in TEI of Athens" project of the "Education & Lifelong Learning" Operational Programme.

Methods and Material

The study considered 71 breast cancer cases of three different grades (I, II or III) collected from the archives of the University Hospital of Patras, Greece. A light microscopy imaging system (LEICA DM 2500 microscope coupled with a LEICA DFC 420C camera, Leica Microsystems GmbH) was used to digitize images from the most representative parts of the tumor, indicated by the expert histopathologists, at 400x and 200x magnifications. The final pattern recognition system was designed using the five different classifiers, the Least Squares Minimum Distance (LSMD), the k-Nearest Neighbor (kNN), the Probabilistic Neural Network (PNN), the Bayesian and the Support Vector Machine (SVM) classifier. Extracted features comprised 22 textural (4 from the grey level histogram, 13 from the grey level co-occurrence matrix and 5 from the grey level run length matrix), 11 morphological (Area, Perimeter, Eccentricity, Major Axis Length, Minor Axis Length, Convex Area, Equivalent Diameter, Solidity, Rectangularity, Compactness and Fractal-Dimension), 6 Shape-based on Boundary (Radial Distance (average), Radial Distance (standard deviation), Radial Distance (range), Circularity Ratio, Entropy Radial Distance, Roughness-Index), 7 from the Minimal Spanning Trees (MST) (average Distance-MST, range Distance-MST, standard deviation Distance-MST, max Distance-MST, min Distance-MST, sum Distance-MST, number of Nodes-MST), 6 Molecular Indices (ER,

PR, cerb2, p53, Ki-67, cath-D) and 2 mammographic features (shading/vagueness of mCa/lesion, mCa/lesion size in mammography).
For the evaluation of the design of the pattern recognition system the leave-one-out, the cross validation and the self-consistency methods were utilized. For feature selection the exhaustive search was applied. For classification five different classifiers were used, the Least Squares Minimum Distance (LSMD), the k-Nearest Neighbors (kNN), the Probabilistic Neural Network (PNN), the Bayesian and the Support Vector Machine (SVM) classifiers (Jain et al., 2000). Also, the software provides a majority vote classifier combination option. For the estimation of the generalization performance of the system to unknown data, the external cross validation method was applied.
Exhaustive search is limited by serious computational and memory limitations. For bypassing these limitations, the CADMAMMO's pattern recognition system was designed on a Graphics Processing Unit (GPU) framework and it is capable of updating its structure in whenever a new verified case is uploaded on its repository.

Results

Results show that the most important single category of features is the textural features on the microscopy images with 87.3% prediction rate. When features from all families were concurrently tested, prediction accuracy was boosted up to 88.7% using a combination of five (5) textural, architectural and radiological features. These features were: 1/Mean Value of the grey level inside nuclei computed to estimate the average intensity over all segmented nuclei for each case, 2/ Information Measure of Correlation-2 (average) that is a relative measure of texture 's entropy that tends to rise along image coarseness, 3/ Maximal Correlation Coefficient (range) is a measure of homogeneity that tends to rise in inhomogeneous images, 4/ Standard deviation of Minimal Spanning Tree is an nuclei topology measure that expresses the variance of nuclei vicinity and tends to decrease with nuclei stacking, plausibly caused by nuclei proliferation in high grade cases, and 5/ mCa/lesion size; microcalcifications are an early stage sign of a potential dangerous lesion. In the presence of a lesion it implies information regarding the degree of abnormality. The combination of microcalcifications with the lesion's size proved significant in discriminating low from high grade breast cancer cases.

Acknowledgements

This research has been co-financed by the European Union (European Social Fund – ESF) and Greek national funds through the Operational Program "Education and Lifelong Learning" of the National Strategic Reference Framework (NSRF) - Research Funding Program: ARCHIMEDES III. Investing in knowledge society through the European Social Fund.

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